1H-PYRAZOLO[1,5-a]INDOLES: ISOELECTRONIC ANALOGUES OF AZULENE (PSEUDOAZULENE)

Jing-Kang SHEN and Hajime KATAYAMA*

Niigata College of Pharmacy, 5-13-2 Kamishin'ei-cho, Niigata, 950-21, Japan

1H-Pyrazolo[1,5-a]indole derivatives were prepared for the first time and found to have the chemical behaviors as the isoelectronic analogues of azulene.

KEYWORDS 1-methyl-1H-pyrazolo[1,5-a]indole; pseudoazulene; 1-methyl-2-phenyl-1H-pyrazolo[1,5-a]indole; azulene isoelectronic

Among the three isomers of 1H-, 3H- and 4H-pyrazolo[1,5-a]indoles, no chemistry has been reported for 1H-isomer (1a, RN=42318-55-8). 1H-Isomer is an interesting compound since it has a condensed indole nucleus and constitutes an 3-aza analogue of the mitomycin's skeletal compound. In this paper we report the first synthesis of 1H-pyrazolo[1,5-a]indole derivatives and their chemical behaviors as the novel isoelectronic analogues of azulene (pseudoazulene).¹⁾

Initially we planned to prepare 1-methyl-2-phenyl-1H-pyrazolo[1,5-a]indole (1c) by the elimination reaction of (2).²⁾ When (2) was reacted with methanesulfonyl(mesyl) chloride in the presence of triethylamine, the sole product was (1e), mp 220-221°C (69% yield by excess reagent) which has one vinylic proton (δ 6.74, s) but also retains mesyl group (δ 3.15, s) according to ¹H-NMR analysis. The formation of (1e), instead of (1c), suggested the high reactivity of 1H-isomer (1c) against electrophilic reagent. In fact, when 1H-isomer (1c), *vide infra*, was reacted with mesyl chloride independently, C-mesylated product (1e) was formed in 89% yield. The position of the mesyl group was assigned when (1d), *vide infra*, was obtained by the same reaction and its adjacent vinylic proton signals appeared at δ 6.43 and 7.27 (each d, J=3.4Hz). The high nucleophilicity of 4-C of 1H-isomer was also demonstrated when 4H-Isomer (3b)³⁾ was treated with butyl lithium and the lithiated product was trapped with acetyl chloride. The product was the diacetylated product (1f), mp 158-159°C (40% yield). Then we turned our attention to the other approach. 4H-Isomer (3b) was methylated with methyl trifluoromethanesulfonate to give the quaternary salt (4b), mp 144-145°C in quantitative yield. The N-methyl group of (4b) appears at δ 4.45 as a singlet. When (4b) was treated with lithium diisopropyl amide, 4-H was removed and the basic product (1c), mp 80-81°C was obtained. This reaction was better effected with sodium hydroxide in ethanol (87% yield). The product (1c) has two vinylic protons at δ 6.15 and 6.44, both as singlets. It has a characteristic UV absorption spectrum at $\lambda_{\max}$ (MeCN) nm (log ϵ): 268 (4.44), 321(3.97), 383(4.02). Similarly (1b), mp 103-104°C was obtained from (4a), mp 181-182°C in 61% yield. This product has three vinylic proton signals at δ 6.09 (s), 6.21(d, J=3.7Hz) and 6.99 (d, J=3.7Hz). The

(1)

a: $R^1=R^2=R^3=H$ b: $R^1=Me, R^2=R^3=H$ c: $R^1=Me, R^2=Ph, R^3=H$ d: $R^1=Me, R^2=H, R^3=Ms$ e: $R^1=Me, R^2=Ph, R^3=Ms$ f: $R^1=R^3=Ac, R^2=Ph$ g: $R^1=Me, R^2=Ph, R^3=CHO$

(2)

(3) a: $R=H$; b: $R=Ph$ (4) a: $R=H$; b: $R=Ph$ (5) a: $R=H$; b: $R=Ph$

1*H*-isomer (1c) was not stable, so that it was transferred into picrate. The ^1H -NMR spectrum of the picrate showed that the protonation took place at 4-C but not at the nitrogen atom. The treatment of (1c) with trifluoromethanesulfonic acid afforded the quaternary salt (4b) in quantitative yield. These transformations mean that the salts (4a) and (4b) are the conjugate acids of the bases (1b) and (1c). When (4b) was reacted with lithium aluminum hydride in ether, (4b) worked as a conjugate acid and (1c) was formed as a sole product. These chemical behaviors of 1*H*-isomer are typical of the isoelectronic analogues of azulene, and the meso-ionic form (5) represents their characters.⁴⁾ The participation of the meso-ionic form is also supported by the ^1H -NMR spectra of 1*H*-isomer (1c) in different solvents (Table I). The increase of the solvent polarity from C_6D_6 to CD_3CN shifted the signals for N-methyl and 3-H to the lower magnetic field. In contrast, 4-H signal moved to the higher magnetic field. However, no remarkable change of UV absorption pattern was observed in these solvents. A similar solvent effect has been reported for 2-ethyl-3-methyl-1-phenyl-1,2-dihydroindeno[2,1-*c*]pyrazole.^{1e)} 1*H*-isomer (1b) and (1c) have similar chemical behaviors to 1,2-dihydroindeno[2,1-*c*]pyrazoles.^{1d,1e)} When (1c) was subjected to the Vilsmeier-Haack reaction, the formyl group (δ 9.93, s) was introduced at 4-C to give (1g). The ^1H -NMR spectra of 1*H*-isomer with the electron-attracting groups at 4-C show the shifts of N-methyl and 3-H signals to the lower magnetic field, as shown in Table II. In 1*H*-isomer (1e) and (1g), the contribution of the meso-ionic forms such as (5) became more important. When deuterium oxide was added to the solution of 1*H*-isomer (1c) in $CDCl_3$, the 4-H signal disappeared from the ^1H -NMR spectrum. No 4-H signal was detected in CD_3OD either. These ready exchanges of 4-H in neutral protic solvent suggest the strong basicity of the 1*H*-isomer (1b), as reported for 1,2,3-trimethyl-1,2-dihydroindeno[2,1-*c*]pyrazole.^{1e)}

Table I. The Solvent Effects of ^1H -NMR Spectra of **1c** (δ)

Solvent	ϵ^*	N-Me	3-H	4-H
C_6D_6	2.2	2.87	6.11	6.34
CDCl_3	4.8	3.50	6.44	6.15
CD_3OD	32.6	3.47	6.52	-
CD_3CN	37.5	3.51	6.54	6.10

* Dielectric constant of proton solvent.

Table II. ^1H -NMR Spectra for **1c, e, g** in CDCl_3 (δ)

Compds	N-Me	3-H
1c	3.50	6.44
1e	3.83	6.74
1g	4.05	6.95

In summary, we were the first to prepare 1*H*-pyrazolo[1,5-*a*]indole derivatives and have demonstrated their peculiar behaviors as the isoelectronics of azulene. The 1*H*-isomer is the novel isoelectronic of azulene (pseudoazulenes) with the nitrogen atom at ring junction. They also constitute the novel skeleton of pyrrolo[1,2-*b*]pyrazole. Their chemical behaviors are best expressed by the meso-ionic forms such as (5).

REFERENCES AND NOTES

- 1) a) R. Mayer, *Angew. Chem.*, **69**, 481 (1958). The first report to refer pseudoazulene; b) Treibs, W. W. Schroth, H. Lichtmann and F. Fischer, *Justus Liebigs Ann. Chem.*, **642**, 97 (1961); c) D. L. Leave, J. Smolicz and W. H. Stafford, *J. Chem. Soc.*, **1962**, 740; d) G. V. Boyd and D. Hewson, *J. Chem. Soc. (C)*, **1968**, 2959; e) K. Hartke and W. Uhde, *Chem. Ber.*, **103**, 2667 (1970).
- 2) This alcohol was derived from 3-hydroxy-2-phenyl-3*H*-pyrazolo[1,5-*a*]indole (J-K. Shen and H. Katayama, *Chem. Lett.*, **1992**, 451) by the oxidation with DDQ and the reduction with lithium aluminum hydride.
- 3) H. Katayama, M. Sakurada, W. H. H. Herath, N. Takatsu and J-K. Shen, *Chem. Pharm. Bull.*, in press.
- 4) The two sets of lone pairs on adjacent nitrogen atoms of 1*H*-isomer can not contribute to form the π -electron systems of pseudoazulene [J. Elguero and R. M. Claramunt, *Adv. Heterocycl. Chem.*, **22**, 183 (1978); H. H. Elnagdi, M. R. H. Elmoghayer, and K. U. Sadek, *Adv. Heterocycl. Chem.*, **48**, 223 (1990)]. But the introduction of meso-ionic form [W. D. Ollis and C. A. Ramsden, *Adv. Heterocycl. Chem.*, **19**, 1 (1976)] allows for these nitrogen lone pairs to constitute the isoelectronic form of azulene.

(Received July 16, 1992)